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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Burchard	Confirmation No.: 6450
Serial No.: 09/616,849	Art Unit: 1634
Filed: July 14, 2000	Examiner: Forman, B.
For: METHOD FOR DETERMINING THE SPECIFICITY AND SENSITIVITY OF OLIGONUCLEOTIDES FOR HYBRIDIZATION	Attorney Docket No: 9301-044

AMENDMENT UNDER 37 C.F.R. §1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed September 25, 2002 in connection with the above-identified patent application and in accordance with Rule 111 of the Rules of Practice, please enter the following amendments and consider the following remarks. Applicant submits herewith: 1) Exhibit A: marked version of amended claims; 2) Exhibit B: clean version of the pending claims; and 3) Amendment Fee Transmittal, accompanied by the appropriate fee.

IN THE CLAIMS:

A marked version of the claims showing the amendments is attached hereto as Exhibit A. Matter that has been deleted from claims 27, 48-54, 67, 75 and 90 is indicated by brackets and matter that has been added is indicated by underlining. A clean version of the pending claims, as amended, is attached hereto as Exhibit B.

Please amend the claims as follows:

Cancel claims 57-58 and 71-72 without prejudice.

Amend claims 27, 48-54, 67, 75 and 90 to read as follows:

27. (Three Times Amended) A method for evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide

sequence, said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe and the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe, wherein:

(a)   the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence; and

(b)   the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence, and wherein said ratio is used as a measure of said binding property, thereby evaluating said binding property of said polynucleotide probe.

48. (Twice Amended) The method of claim 43 wherein each said polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than a factor of 100.

49. (Twice Amended) The method of claim 43 wherein each said polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than a factor of 10.

50. (Twice Amended) The method of claim 43 wherein each said polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than 50%.

51. (Twice Amended) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first

sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than a factor of two.

52. (Twice Amended) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 50%.

53. (Twice Amended) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 10%.

54. (Twice Amended) The method of claim 43 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 1%.

57. (Three Times Amended) The method of claim 38, 40 or 43 wherein said binding property is a specificity of the polynucleotide probe, wherein said specificity is the amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe relative to the amount of polynucleotide molecules not comprising said target nucleotide sequence that bind to the probe under the same binding conditions.

67. (Three Times Amended) A method for evaluating a binding property of a plurality of polynucleotide probes to a target nucleotide sequence wherein each polynucleotide probe in the plurality of polynucleotide probes comprises a predetermined nucleotide sequence,

said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes and the amount of hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes, wherein:

(a)   the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence; and

(b)   the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a nucleotide sequence that is different from nucleotide sequence of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence, and wherein said ratio is used as a measure of said binding property, thereby evaluating said binding property of each said polynucleotide probe.

75. (Twice Amended) The method of claim 67 wherein the first sample comprises two or more different polynucleotide molecules

wherein none of the two or more different polynucleotide molecules hybridizes or cross-hybridizes to a probe that also hybridizes or cross-hybridizes to another one of the two or more different polynucleotide molecules.

90. (Amended) The method of any one of claims 27-30, 33-40, 42-54, 61-68, 73-75 and 84-85, wherein said polynucleotide molecules comprising said target nucleotide sequence are the same polynucleotide molecule.

Add new claims as follows:

91. (New) A method for evaluating a binding property of a plurality of polynucleotide probes to a target nucleotide sequence, said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes and the amount of hybridization of polynucleotides in a

second sample to each polynucleotide probe in the plurality of polynucleotide probes, wherein:

(a)   said first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and a plurality of polynucleotide molecules that do not comprise the target nucleotide sequence; and

(b)   said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequence of any other polynucleotide molecule in said plurality of different polynucleotide molecules, and wherein each different polynucleotide molecule in the second sample does not comprise the target nucleotide sequence

wherein each polynucleotide probe in the plurality of polynucleotide probes comprises a predetermined nucleotide sequence and wherein said ratio is used as a measure of said binding property, thereby evaluating said binding property of said plurality of polynucleotide probes.

92. (New) The method of claim 91 wherein:

(a)   said target nucleotide sequence is a sequence of a gene or gene transcript of a cell or organism;

(b)   said first sample comprises a polynucleotide sample from a wild-type strain of the cell or organism which expresses the gene or gene transcript; and

(c)   said second sample comprises a polynucleotide sample from a deletion mutant of the cell or organism that does not express the gene or gene transcript.

93. (New) A method for evaluating a binding property of a plurality of polynucleotide probes to a target nucleotide sequence, said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes and the amount of hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes, wherein:

(a)   said first sample comprises a plurality of polynucleotide molecules comprising

said target nucleotide sequence and a plurality of polynucleotide molecules

that do not comprise the target nucleotide sequence; and

(b)   said second sample comprises a plurality of different polynucleotide molecules

wherein each different polynucleotide molecule comprises a sequence that is

different from the nucleotide sequence of any other polynucleotide molecule in

said plurality of different polynucleotide molecules,

wherein each polynucleotide probe in the plurality of polynucleotide probes comprises a

predetermined nucleotide sequence and wherein said ratio is used as a measure of said

binding property, thereby comparing said binding property of said plurality of polynucleotide

probes.

94. (New) The method of claim 93 wherein:

(a)   said target nucleotide sequence comprises a sequence of a gene or gene

transcript of a cell or organism; and

(b)   said second sample comprises a polynucleotide sample from a wild-type strain

of said cell or organism, wherein the wild-type strain of the cell or organism

expresses the gene or gene transcript.

95. (New) The method of claim 93, wherein said second sample comprises:

(b1)   polynucleotide molecules comprising the target nucleotide sequence,

and

(b2)   a plurality of different polynucleotide molecules, each different

polynucleotide molecule comprising a different nucleotide sequence

and not comprising the target nucleotide sequence,

and wherein the amount of polynucleotide molecules in said first sample comprising the

target nucleotide sequence differs by at least a factor of two from the amount of

polynucleotide molecules in said second sample comprising the target nucleotide sequence.

96. (New) The method of claim 95 wherein the amount of polynucleotide molecules

in said first sample comprising said target nucleotide sequence differs from the amount of

polynucleotide molecules in said second sample comprising said target nucleotide sequence

by at least a factor of four.

97. (New) The method of claim 95 wherein the amount of polynucleotide molecules in said first sample comprising said target nucleotide sequence differs from the amount of polynucleotide molecules in said second sample comprising said target nucleotide sequence by at least a factor of eight.

98. (New) The method of claim 95 wherein the amount of polynucleotide molecules in said first sample comprising said target nucleotide sequence differs from the amount of polynucleotide molecules in said second sample comprising said target nucleotide sequence by at least a factor of twenty.

99. (New) The method of claim 95 wherein the amount of polynucleotide molecules in said first sample comprising said target nucleotide sequence differs from the amount of polynucleotide molecules in said second sample comprising said target nucleotide sequence by at least a factor of 100.

100. (New) The method of claim 95 wherein each said polynucleotide molecule that does not comprise said target nucleotide sequence in said first sample is present in said second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than 50%.

101. (New) The method of claim 95 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than a factor of two.

102. (New) The method of claim 95 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not

comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 50%.

103. (New) The method of claim 95 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 10%.

104. (New) The method of claim 95 wherein the mean abundance of the polynucleotide molecules that do not comprise the target nucleotide sequence in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 1%.

REMARKS

Claims 27-30, 33-40, 42-54, 57-68, 71-75, 84-85 and 90 were pending in the application. In the instant amendment, claims 57-58 and 71-72 have been canceled without prejudice, claims 27, 48-54, 67, 75 and 90 have been amended, and new claims 91-104 have been added to more clearly claim the present invention. Upon entry of the above-made amendment, claims 27-30, 33-40, 42-54, 59-68, 73-75, 84-85 and 90-104 will be pending. A marked version of the amended claims showing changes made is attached hereto as Exhibit A. A clean version of the pending claims, as amended, is attached hereto as Exhibit B.

Claims 27 and 67 have been amended to recite that the claimed method comprises determining *a ratio of* the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe and the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe, and that the ratio *is used as a measure of said binding property* (emphasis added). Support for the amendment is found in the specification at page 40, line 30, through page 41, line 36; and page 48, line 28, through page 49, line 11.

Claim 51 has been amended to clarify that in the claimed method, the mean abundance of polynucleotide molecules that do not comprise the target nucleotide sequence in

the first sample differs from the mean abundance of the different polynucleotide molecules *that do not comprise the target nucleotide sequence* in the plurality of different polynucleotide molecules of the second sample by no more than a factor of two (emphasis added). Claims 52-54 have been amended similarly. Claim 54 has also been amended to clarify that in the claimed method, the mean abundance of the polynucleotide molecules *that do not comprise the target nucleotide sequence* in the first sample differs from the mean abundance of the different polynucleotide molecules that do not comprise the target nucleotide sequence in the plurality of different polynucleotide molecules of the second sample by no more than 1% (emphasis added). Support for the amendment is found in the specification at page 32, line 6, through page 34, line 15.

Claims 48-50, 75 and 90 have been amended to make the claim language clearer.

New claims 91-104 have been added. Support for the new claims is found in the specification at page 44, lines 27-32; page 6, line 13, through page 7, line 33; and page 32, line 6, through page 34, line 15.

No new matter has been added by these amendments. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

Claims 1, 48-50, 75 and 90 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In paragraph 4a of the Office Action, claims 48-50 are rejected as allegedly being indefinite for the recitation of "differs from the amount of the corresponding polynucleotide molecules" because "corresponding" is a non-specific relational term. Applicant has amended claim 48 to recite that in the claimed method each said polynucleotide molecule that does not comprise the target nucleotide sequence in the first sample *is present in the second sample in an amount that differs from the amount of said polynucleotide molecule in the first sample by no more than a factor of 100* (emphasis added). Claims 49 and 50 have been amended similarly. The rejection is therefore obviated and should be withdrawn.

In paragraph 4b of the Office Action, claim 75 is rejected as allegedly being indefinite for the recitation of "wherein none of the plurality of different polynucleotide molecules"

NY2 - 1381850.1

because it is unclear whether the recitation refers to the "two or more" in claim 75 or the "plurality of different polynucleotide molecules" in claim 67. Applicant has amended the claim to clarify that the recitation refers to the two or more different polynucleotide molecules as recited in the first line of claim 75. The rejection is therefore obviated and should be withdrawn.

In paragraph 4c of the Office Action, claim 90 is rejected as allegedly being indefinite for the recitation of "wherein said polynucleotide molecules comprising said target nucleotide sequences are the same." Applicant has amended the claim to clarify that the polynucleotide molecules comprising said target nucleotide sequences are the same polynucleotide molecule. The rejection is therefore obviated and should be withdrawn.

<u>THE REJECTION UNDER 35 U.S.C. § 102(b)</u>
<u>SHOULD BE WITHDRAWN</u>

Claims 27-30, 33-40, 42-54, 57-68, 71-75, 84-85 and 90 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lockhart et al., U.S. Patent No. 6,344,316 ("Lockhart"). Applicant respectfully disagrees with the Examiner for the reasons presented below.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.,* 52. F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

Lockhart teaches methods for identifying differences in nucleic acid abundances (e.g., expression levels) between two or more samples using high density DNA microarrays. In Lockhart, a method of optimizing a set of probes for detection of a particular gene is also disclosed. The probe optimization method involves first hybridizing the probes with their target nucleic acid alone and then hybridizing the probes with a high complexity, high concentration nucleic acid sample that does not contain the targets complementary to the probes, and selecting those probes that show a strong hybridization signal with their target and little or no cross-hybridization with the high complexity sample as preferred probes for use in the high density arrays. For selection of probes showing strong hybridization signal with their target, Lockhart teaches that the probes are hybridized to a sample containing target

nucleic acids having subsequences complementary to the oligonucleotide probes, and that those probes are selected for which the difference in hybridization intensity between the probes and their respective mismatch controls for hybridization to the same sample exceeds a threshold hybridization intensity (see, e.g., Lockhart col. 37, lines 1-12). For selection of probes showing little or no cross-hybridization, Lockhart teaches that the probes can be hybridized with a nucleic acid sample that is not expected to contain sequences complementary to the probes, and that those probes for which both the probes and their mismatch controls show hybridization intensities below a threshold value are selected (see, e.g., Lockhart col. 37, lines 13-23). Thus, in Lockhart, selection of probes that show a strong hybridization signal with their target and little or no cross-hybridization is achieved by evaluating a probe according to its hybridization abilities to the target sample and to the non-target sample separately and comparing the hybridization abilities to the target sample and to the non-target sample to the respective threshold separately. Lockhart does not teach that a ratio of the amount of hybridization by a first sample, e.g., a specific hybridization sample, to a polynucleotide probe and the amount of hybridization of a second sample, e.g., a non-specific hybridization sample, to the polynucleotide probe can be used as a measure of a binding property of the probe. Nor does Lockhart teach a method of evaluating the binding property of a probe by determining such a ratio as required by claims 27 and 67, as amended, and the claims dependent thereon. Therefore, Applicant respectfully submits that Lockhart does not anticipate claims 27-30, 33-40, 42-54, 59-68, 73-75, 84-85 and 90, as amended, and that the rejection under 37 C.F.R. § 102(b) based on Lockhart should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 37-40, 42, 43, 48-54, 84-85 and 90 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lockhart et al., U.S. Patent No. 6,344,316 ("Lockhart") in view of Brown et al., U.S. Patent No. 5,807,522 ("Brown"). Applicant respectfully disagrees with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether

NY2 - 1381850.1

the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Rouffet, 149 F.3d 1350* (Fed. Cir. 1998).

Lockhart has been discussed above. Brown teaches methods and apparatuses for forming microarrays of cDNAs on a support. Brown also teaches hybridization of nucleic acid samples to its microarrays. For example, in its example 1, Brown teaches hybridization to its microarray of two pools of nucleic acids, in which one pool contains random amplification products of the 6 large yeast chromosomes and the other pool contains random amplification products of the 10 small yeast chromosomes. The hybridization values of spots or clones on the array identify to which of the two pools the clones belong and correlate the clone to the location on the yeast genome (see, e.g., Brown, col. 17, lines 3-40).

At the outset, Applicant respectfully points out that, as discussed above, in Lockhart, selection of probes that show a strong hybridization signal with their target and little or no cross-hybridization is achieved by evaluating a probe according to its hybridization abilities to the target sample and to the non-target sample separately and comparing the hybridization abilities to the target sample and to the non-target sample to the respective threshold separately. Lockhart does not teach that a ratio of the amount of hybridization by a first sample, e.g., a specific hybridization sample, to a polynucleotide probe and the amount of hybridization by a second sample, e.g., a non-specific hybridization sample, to the polynucleotide probe can be used as a measure of a binding property of the probe. Nor does Lockhart teach a method of evaluating the binding property of a probe by determining such a ratio. Brown does not teach or suggest evaluating a binding property of a polynucleotide probe, much less using a ratio of the amount of hybridization by a first sample, e.g., a specific hybridization sample, to a polynucleotide probe and the amount of hybridization of by a second sample, e.g., a non-specific hybridization sample, to the polynucleotide probe as a measure of a binding property of the probe. Thus, Brown does not supply what is missing in Lockhart.

With respect to specific rejections, Applicant first respectfully points out that the

Examiner's rejections of claims 37, 38, 40, 42, 43, and 48-54 are based on a contention that Lockhart's probe selection scheme can be modified by replacing one or both of Lockhart's samples with Brown's sample or samples so as to render the presently claimed method obvious. Applicant submits that such a contention is erroneous in that even if Brown's samples are used in conjunction with Lockhart's probe selection scheme, the combination would still be a sequential probe selection method in which the hybridization data to the target sample and to the non-target sample are compared to a respective threshold value separately. Thus, Applicant respectfully submits that Lockhart cannot be modified by Brown as suggested by the Examiner to give rise to the presently claimed invention.

Applicant also respectfully points out that the Examiner's rejection of claim 84 is based on a contention that Lockhart can be modified by replacing Lockhart's sequential hybridization with Brown's concurrent hybridization so as "to hybridize the first and second samples to the probes concurrently thereby eliminating Lockhart's second hybridization step for the obvious benefits of simplification and economy of time by replacing one or both of Lockhart's samples used with Brown's sample or samples." Applicant submits that such a contention is erroneous in that the contended combination does not render the present invention obvious. As discussed above, in Lockhart, selection of probes that show a strong hybridization signal with their target and little or no cross-hybridization is achieved by evaluating a probe according to its hybridization abilities to the target sample and to the non-target sample separately and comparing the hybridization abilities to the target sample and to the non-target sample to the respective threshold separately. Therefore, Lockhart's sequential probe selection method includes not only sequential hybridization as agreed by the Examiner, but also separate or sequential comparing procedures utilizing the obtained hybridization data. Even were the hybridization data to be measured concurrently, to perform probe selection, hybridization data to the target sample and to the non-target sample would still be used separately. Thus, Applicant respectfully submits that such modification of Lockhart by Brown as suggested by the Examiner does not suggest the presently claimed invention.

With respect to claims 39, 85 and 90, the Examiner contends that Lockhart teaches or suggests using in its probe selection method one or both samples as taught by the presently claimed method. Applicant respectfully submits that, as discussed above, Lockhart does not teach or suggest that a ratio of the amount of hybridization by a first sample, e.g., a specific

NY2 - 1381850.1

hybridization sample, to a polynucleotide probe and the amount of hybridization of by a second sample, e.g., a non-specific hybridization sample, to the polynucleotide probe can be used as a measure of a binding property of the probe. Nor does Lockhart teach a method of evaluating the binding property of a probe. Thus, the difference between Lockhart and the presently claimed invention does not rest on differences in samples used. As such, Lockhart does not render claims 39, 85 and 90 obvious irrespective of whether the samples used are different or not.
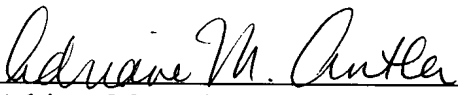
Therefore, Applicant respectfully submits that the rejection of claims 37-40, 42, 43, 48-54, 84-85 and 90 under 35 U.S.C. § 103(a) based on Lockhart and Brown should be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks into the file of the above-identified application. Applicant believes that each ground for rejection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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Enclosures

- 14 -